AGE CYCLES AND OTHER PERIODICITIES IN ORGANISMS.

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According to the group of biological theories of which the Weismannian theory is the best example, the process of aging is irreversible and progresses always in one direction. Young individuals arise from the germ plasm, that fountain of perpetual youth, and once started on the path of development there is no turning back for them but they go on inevitably toward the one end—death. These theories neglect, however, to tell us why a part of the living protoplasm of a species should differentiate, grow old and die and another part remain perpetually young, and why, once started on the downward path, there is no possibility of return for the developing organism.

Within recent years the suggestion has been made more than once that development may be a reversible process and the fact has been established beyond doubt, that at least many cells, even in the higher animals, may undergo more or less dedifferentiation as well as differentiation. Since aging or senescence is very evidently closely associated somehow with the processes of development and differentiation we are then brought face to face with the question; can cells or organisms grow young as well as grow old? If rejuvenescence as well as senescence is a characteristic feature of life then we must expect to find that young cells or organisms arise, not from a perpetually young germ plasm, but from old cells or organisms through changes in the opposite direction from those which constitute senescence. Life from this point of view is then a cycle consisting of alternating periods of senescence and rejuvenescence. If such age cycles exist, we should expect to find them in their simplest terms in the simple organisms, and in my own experimental attack on this problem I have been primarily concerned with these simple organisms.

It has long been known that in the higher animals and man the most characteristic physiological feature of the process of senescence is a progressive decrease in the rate of metabolism, or of certain fundamental metabolic reactions from birth and undoubtedly from still earlier stages onward. This is accompanied, as Minot and others have shown, by a decrease in the rate and final cessation of growth.

In my own experiments on the lower animals I have found that a similar decrease in metabolic rate and rate of growth occurs during the life history. A very simple method has made it possible to use the metabolic condition to a very large degree as a criterion of physiological age. This method depends on the fact that the susceptibility to many, if not all, agents which kill by decreasing metabolism in one way or another, varies with the general metabolic rate. In concentrations of such agents which kill in the course of a few hours the individual with the higher metabolic rate is the more susceptible and dies sooner than the individual with lower rate. This method has been checked and controlled by various others in many ways and can be used very widely for comparing the metabolic condition of different individuals among the lower organisms.

I have found that the general metabolic rate in the simple animals, particularly in certain of the planarian worms which have been the chief experimental material, decreases from a very early stage of development on through life, as growth and development proceed. A progressive decrease in rate of growth also indicates that these animals undergo senescence.

These planarians undergo a process of fission in nature in which the posterior body region separates off and becomes a new individual, but we do not need to wait for the occurrence of such fission, for we can induce the development of new individuals by cutting the animals into pieces. Each piece develops a head at its anterior end, a tail at its posterior end, and undergoes more or less dedifferentiation and internal reorganization and usually develops into a new whole with the characteristic structure of the species, but of smaller size than the individual from which the piece was taken, the size of the new individual depending on the size of the piece. In undergoing this reconstitution the piece uses up a part of its own body substance as a source of energy and of the new cell material formed.

A test of the metabolic condition of the new individual thus formed shows that it is physiologically younger than the animal from which the piece was taken, and the smaller the fraction of the original body from which it developed, the younger it is. By feeding it can be made to grow, to go through the life history and to become old again, and may then again be cut into pieces which once more become young individuals, and this process can be carried on for a long time, probably indefinitely. I have carried an experiment of this sort through twenty generations. Evidently the process of reconstitution of these pieces into new animals in some way brings about a greater or less degree of rejuvenescence.

Another experiment affords a clue as to the manner in which this rejuvenescence occurs. If the full-grown planarians which are 25–30 mm. in length are deprived of food, they do not die of starvation in a few days, but gradually become smaller, and can be reduced to a length of a millimeter or less before death occurs. Tests of metabolic condition show that during this reduction the metabolic rate is increasing, the animals are growing younger. Morphologically also they show indications of rejuvenescence. By feeding we can stop this process of rejuvenescence at any time and make the animals begin to grow old again, and we can repeat this process again and again.

In another species of planarian in which the length of the life cycle under ordinary conditions in nature is about two months, I have been able to keep the same individual worms alive and in essentially the same physiological condition for a much longer period than the usual length of life, simply by regulating quantity and quality of food, *i. e.,* the animals were fed just enough of the food, found by experience to be most suitable, to prevent reduction in size and not enough to permit growth. With this procedure they remained in practically the same physiological condition, of the same physiological age during nearly four years, while other members of the same original stock, fed in the usual way, passed through some twenty generations.

These experiments afford some insight into the nature of the process of senescence and rejuvenescence. We see that when the animal is adding to its protoplasmic substratum by growth and transforming it by processes of differentiation it is growing old, but when it is using up previously formed protoplasmic material, as it does in reconstitution and starvation, it is growing young. In the simple animals where the structural substratum of the body built up under one sort of conditions is readily broken down under other conditions in the absence of nutrition, or in reconstitution, rejuvenescence occurs readily and may carry the animal back almost to embryonic stages, but the evolution of the higher forms is very evidently associated with a physiological stabilization of the structural substratum of the body and we find that in man and the mammals bodily rejuvenescence is apparently limited. A large part of the structural substratum is either not available for nutritive purposes or cannot be broken down rapidly enough to supply the demands, and death occurs before any great degree of rejuvenescence has taken place in the body as a whole. But that some slight degree of bodily rejuvenescence may occur even in man cannot be doubted.

It is impossible to consider here all the various lines of evidence, but it may be said that the facts at present available indicate that senescence consists in a decrease in metabolic rate determined by the changes in, and the progressive accumulation of, the relatively stable components of the protoplasmic substratum during growth, development and differentiation. Rejuvenescence, on the other hand, is an increase in metabolic rate determined by the breakdown of previously accumulated structural substances in dedifferentiation, starvation and reproduction and the development of new protoplasmic substance in place of that eliminated. We may say, in short, that the organism grows old when the primitive embryonic protoplasmic substratum is modified or added to by changes in the colloids and accumulation of relatively stable components by growth and differentiation, so that the protoplasm becomes less active chemically, and that it grows young when the protoplasm previously thus modified loses these modifications to a greater or less extent and approaches or attains the primitive undifferentiated or embryonic condition and becomes more active chemically. The youngest protoplasm is protoplasm reduced to its lowest terms as a colloid substratum of chemical reaction and aging occurs as this protoplasm is modified by changes in the colloids and accumulation of relatively inactive substance.

In the lower animals the processes of asexual reproduction are essentially similar to the reconstitution of pieces experimentally isolated and all such processes are accompanied by some degree of rejuvenescence. Even in the unicellular animals, I have found that every cell division with its accompanying processes of reorganization, giving rise to a new individual is accompanied by some increase in metabolic rate, *i. e.*, some degree of rejuvenescence. Under certain conditions senescence and rejuvenescence may balance each other and asexual reproduction may continue indefinitely, while under other conditions the degree of rejuvenescence may not be sufficient to balance senescence in each generation, and in such cases a progressive race senescence occurs.

Turning now to sexual or gametic reproduction, we must inquire how it is related to the age cycle. The facts are these: the sex cells develop only at a very advanced stage of the senescence period of the individual, and in many of the lower animals sexual maturity can be experimentally prevented by keeping the animals physiologically young through asexual reproduction or reconstitution or even periodic starvation. If the sex cells are perpetually young, undifferentiated cells it is not easy to account for the relation between sexual maturity and advanced physiological age.

As regards their morphological structure, the sex cells are among the most highly differentiated and specialized cells in the organism. The period of their development from the mother germ cells is a period of growth and differentiation like that of the other parts of the organism during development. Physiologically also this period is a period of decreasing metabolic rate, of senescence in all cases thus far examined. In short, both morphological and physiological evidence force us to the conclusion that the mature sex cells or gametes are highly differentiated, physiologically old cells.

It has been shown by Loeb, Warburg and others, that an increase in the rate of oxidation follows fertilization and Warburg has shown further that an acceleration of the oxidation-rate continues through the cleavage stages and at least to the swimming larval stage in the sea urchin. I have found that in all forms examined thus far, including echinoderms, annelids, fishes and amphibia, the increase in susceptibility during early development indicates that the rate of metabolic reaction increases up to a certain stage of development and then begins to decrease. All the facts at hand then indicate that the early period of embryonic development is a period of physiological rejuvenescence. Morphologically also it is a period of dedifferentiation. The highly specialized structure of the egg is lost and the cells gradually become undifferentiated or embryonic in appearance.

In fact the evidence indicates very clearly that the sexual reproductive cells or gametes represent the final stages in a period of differentiation and senescence, that their union initiates a process of rejuvenescence which continues through the early stages of embryonic development and is followed again, as the differentiation and accumulation of structural substance overbalance dedifferentiation and reduction, by a period of senescence which may be practically continuous throughout the life of the individual as in the higher animals and man, or which may be interrupted or balanced by periods of rejuvenescence connected with asexual reproduction and other processes, as in many lower forms. The stage of most extreme youth is not then at the beginning of embryonic development but at some later stage, varying in different animals and in different tissues of the same body.

If these conclusions are correct there is no germ plasm in the sense of a perpetually young protoplasm handed on from generation to generation, but the organism undergoes growth, differentiation and senescence as a whole and in both asexual and sexual reproduction rejuvenescence occurs. In the higher animals and man sexual reproduction is the only process and the sex cells the only cells in which any very great degree of rejuvenescence occurs in nature, but in the lower forms all cells of the body may undergo rejuvenescence as well as senescence in asexual reproduction, starvation, and various other processes. Even in the mammals and man, however, evidence is accumulating that at least many of the tissue cells may undergo a considerable degree of dedifferentiation and rejuvenescence under proper conditions and with the further development of experimental technique we may expect further evidence along this line.

If this point of view is correct, life, so far as age is concerned, is a periodic cycle in which senescence alternates with rejuvenescence. The periods of growth and differentiation, in short of development, are the periods of senescence, the periods of dedifferentiation and reduction, the periods of rejuvenescence. It can be shown further that in at least many cases the process of senescence by decreasing the effectiveness of the physiological integrating factors in the individual leads automatically and necessarily to the physiological isolation of parts and so to reproduction of one sort or another and rejuvenescence. The sequence of the two periods follows necessarily from the constitution of protoplasm. The period of senescence is the period of accumulation and decreasing dynamic activity, and in the highly integrated individual it may end in the death of some or most parts. In any case, however, the period of senescence leads in one way or another to the physiological isolation of cells or multicellular parts, as I have shown elsewhere,[1] and these, if they are capable of continued existence after such isolation, undergo dedifferentiation just as the piece experimentally isolated from the planarian body undergoes dedifferentiation, because the conditions which previously maintained differentiation are no longer present and the supply of nutrition is cut off. If the isolated part lives, it lives at the expense of its own substance and the portions of it which required the special conditions resulting from the physiological association with other parts for their formation and maintenance are the first to break down and serve as a

[1] Child, "Individuality in Organisms," Chicago, 1915.

source of energy. In this way the isolated part undergoes a process of dedifferentiation and in so doing becomes physiologically younger and approaches or attains the generalized or undifferentiated condition of that particular protoplasm. If sufficient energy is available in the form of nutrition, either from its own substance or from its environment, this period of dedifferentiation is followed by a new period of differentiation and senescence. In other words, from being a differentiated, specialized part it becomes an undifferentiated or generalized whole by the loss of its specialized features and then undergoes a new course of specialization as its constitution determines.

In the evolutionary adjustment between the period of rejuvenescence and environmental conditions natural selection has unquestionably played an important part, for it is evident that no species can persist from generation to generation in which a source of nutrition is not available in time to save the parts concerned in reproduction from death by starvation. If this were not the case the period of dedifferentiation and rejuvenescence would end in death, as in the case of the starving planarian. Rejuvenescence may follow senescence automatically, but for a new period of senescence following the rejuvenescence, nutrition from without is sooner or later necessary.

We must now inquire whether this age cycle is unique in organic life or whether there are other periodicities which in any way resemble it. I believe there are many other periodicities of essentially similar character. Fatigue, for example, as distinguished from exhaustion, results from the accumulation of substances which retard metabolism and recovery, from the removal of these substances. The chief difference between this periodicity and the age cycle is that the substances which produce fatigue are products of catabolism, essentially waste products and that they are soluble and readily removed, while in age they are essential constituents of the differentiating protoplasmic substratum.

Again, the period of so-called loading of the gland cell is a period of decreasing metabolism and accumulation of substance with marked change of structures in the cell and resembles the period of senescence except that it may take place in a few hours. The loaded gland cell, like the egg, usually requires stimulation before it is able to initiate the process of discharge, but, once begun, this process undergoes acceleration, the metabolic rate rises, the cell loses its peculiar structure and becomes less specialized in appearance. This is comparable to a period of rejuvenescence, and in the presence of nutritive material this period is again followed by a period of loading and decreasing metabolic rate.

In the green parts of a plant in the presence of light and carbon dioxide loading of the cells with starch and a progressive decrease in activity occurs, while in darkness the starch may be transformed to sugar and carried to other parts, and the cells regain their former condition.

Again in seasonal and other periodicities similar alternations appear, a period of accumulation and decreasing dynamic activity is followed by a period of quiescence in which recovery gradually occurs or after which activity may rapidly increase when external conditions such as temperature permit. Periods of encystment following growth and accumulatory periods in the lower organisms, and periods of hibernation or estivation following periods of active nutritive intake are to a greater or less degree essentially periods of rejuvenescence.

In many of these cases the beginning of the period corresponding to rejuvenescence is determined by environmental rather than internal factors but this is incidental. The progressive period instead of proceeding to its natural termination is interrupted, and a regressive period initiated by external conditions. The organism in such cases merely responds to the rhythms in its environment, but such responses are minor periodicities which show certain resemblances to the periodicity of the age cycle. The course of life is then a complex periodic curve made up of many periodicities of various lengths, the normal age cycle being the longest for the individual.

But in conclusion, we may at least raise the question whether there are not periodicities of this sort extending beyond the life of the individual. Is there not evidence in favor of the view that evolution is a secular senescence of protoplasm, interrupted here and there by periods of rejuvenescence? Such periods of evolutionary rejuvenescence if they have occurred, have probably, like some of the minor periods in the life of an individual, been determined by environmental factors, for the natural, internally determined period of secular protoplasmic senescence has not yet reached its termination. In any case the general similarity between evolutionary and individual differentiation suggests that similar factors are at work in both cases, and since the period of individual differentiation is in general a period of senescence, the suggestion that something of similar character is occurring in evolution is not wholly unwarranted.

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